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Prenatally Diagnosed De Novo Apparently Balanced Complex Chromosome Rearrangements: Two New Cases and Review of the Literature

C. Ruiz, R.E. Grubs, T. Jewett, K. Cox-Jones, E. Abruzzese, M.J. Pettenati, and P.N. Rao

Section on Medical Genetics, Department of Pediatrics, The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina

Complex chromosome rearrangements (CCR) are rare structural rearrangements. Currently six cases of prenatally diagnosed balanced de novo CCR have been described. We present two new cases of prenatally ascertained balanced de novo CCR. In the first case, an amniocentesis revealed a balanced de novo three-way CCR involving chromosomes 5, 6, and 11 with a pericentric inversion of chromosome 5 [four breaks]. In the second case, a balanced de novo rearrangement was identified by amniocentesis which involved a reciprocal translocation between chromosomes 3 and 8 and a CCR involving chromosomes 6, 7, and 18 [six breaks]. The use of whole chromosome painting helped elucidate the nature of these rearrangements. A review of the postnatally ascertained cases suggests that most patients have congenital anomalies, minor anomalies, and/or developmental delay/mental retardation. In addition, there appears to be a relationship between the number of chromosome breaks and the extent of phenotypic effects. The paucity of information regarding prenatally diagnosed CCR and the bias of ascertainment of postnatal CCR cases poses a problem in counseling families. © 1996 Wiley-Liss, Inc.

KEY WORDS: complex chromosome rearrangements, de novo, prenatal diagnosis

INTRODUCTION

Complex chromosome rearrangements (CCR) are defined as chromosome rearrangements involving more than two chromosome breaks and the reciprocal exchange of segments between at least two chromosomes [Pai et al., 1980; Kleczkowska et al., 1982]. CCR can be further categorized into two groups based on the number of chromosome breaks, those with four or fewer breaks (group I) and those with more than four breaks (group II) [Kousseff et al., 1987]. Congenital CCR are rare structural rearrangements which are clinically different than acquired CCR often observed in patients with cancer or leukemia.

Most individuals with congenital CCR have been ascertained because of mental retardation, multiple congenital anomalies, recurrent pregnancy loss, or infertility. Only a few cases have been ascertained prenatally. We present two new cases of prenatally diagnosed de novo apparently balanced CCR. The utilization of whole chromosome painting in conjunction with conventional cytogenetics helped elucidate the nature of the rearrangements. A review of postnatally ascertained balanced de novo CCR is also presented with a comparison to the cases ascertained prenatally.

MATERIALS AND METHODS

Cytogenetics

Conventional GTG-banded chromosome studies were performed on routinely processed amniotic fluid samples and peripheral blood using standard laboratory techniques. A total of 20 GTG banded metaphases were examined with the complete analysis of four karyotypes. Standard ISCN nomenclature was used with each analysis.

Whole Chromosome Painting (WCP)

In order to identify any subtle chromosome rearrangements VYSIS (Downers Grove, IL) WCP™ DNA probe kits for chromosomes 5, 6, and 11 were used individually on peripheral blood metaphases corresponding to the chromosomes involved in each case. The methodology was essentially that of the manufacturer.

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Address reprint requests to Cristina Ruiz, Department of Pediatrics, Section on Medical Genetics, Bowman Gray School of Medicine of Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157.

CASE REPORTS AND RESULTS

Patient A

Clinical. A 34-year-old G_3P_2 woman underwent amniocentesis at 16.5 weeks gestation due to an increased risk for Down syndrome based on MSAFP/hCG screening. Amniocentesis showed an apparently balanced complex chromosome rearrangement involving chromosomes 5, 6, and 11. Parental chromosomes were normal. Based on the cytogenetic findings the couple was counseled about the increased risk for some phenotypic affect including mental retardation and/or congenital anomalies. The couple opted to continue the pregnancy. Pregnancy history was unremarkable with the exception of extreme nausea from 5 to 32 weeks gestation. There was no history of exposures to radiation or other teratogens.

Several ultrasound evaluations were performed because of decreased fundal height for dates but no identifiable defects were observed. The propositus was born at 40 weeks of gestation by induced vaginal delivery secondary to maternal hypertension with a birth weight of 2,273 g and a birth length of 45.7 cm. The baby was noted to have hypoglycemia and was admitted to the intermediate nursery. During that time, the child had hyperbilirubinemia which did not require phototherapy.

Physical examination by a clinical geneticist at 2½ months of age did not evidence any major malformations. Several minor anomalies were observed: a prominent forehead with some asymmetry, depressed nasal bridge, anteverted nares, undescended right testicle, mild fifth finger clinodactyly, prominent cutis marmorata, and diffuse hypotonia. In addition, height and weight were below the 5th centile with a head circumference at the 5th centile. At 3 months a developmental evaluation demonstrated age-appropriate skills in all areas of development. At 9 months of age he remained appropriate developmentally and his hypotonia had resolved. At that time his length and weight still remained below the 5th centile. This may be familial since his two older sisters were also reported to be near the 5th centile in height and weight.

Cytogenetic. Karyotypic analysis on cultured amniocytes revealed a CCR involving a single break on chromosomes 6 and 11, and two breaks on chromosome 5 including a pericentric inversion: 46,XY,t(5;6;11)(5pter→5p15::5q21→5p15::6q15→6qter;6pter→6q15::11p11.2→11pter;5qter→5q21::11p11.2→11qter) (Fig. 1). Peripheral blood cytogenetic analysis confirmed the prenatal diagnosis of a de novo CCR.

Whole chromosome painting. Chromosome painting with chromosome 5, 6, and 11 specific libraries confirmed the presence of chromosome 6 on the long arm of chromosome 5, chromosome 5 on the short arm of chromosome 11, and chromosome 11 on the long arm of chromosome 6 (Fig. 2A,B,C). The chromosome 5 paint was particularly useful in confirming the origin of the inverted segment and the translocation between chromosomes 5 and 11.

Patient B

Clinical. A $G_3P_1A_1$ 36-year-old woman and her husband were referred for amniocentesis due to advanced maternal age. Pregnancy history was unremarkable for teratogenic or clastogenic agents. An amniocentesis at 14.9 weeks gestation showed a complex chromosome re-

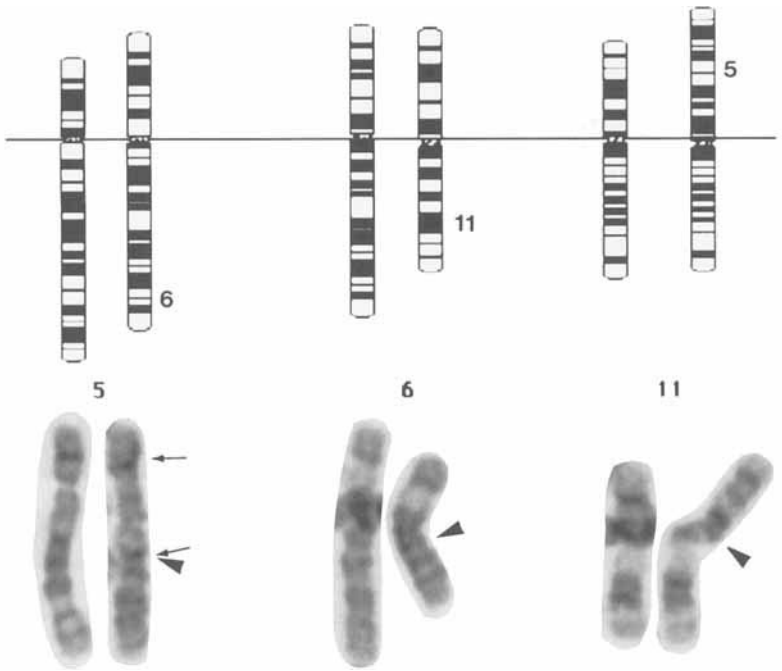

Fig. 1. Patient A: partial G-banded karyotype showing normal chromosomes 5, 6, and 11, and complex chromosome rearrangement. Arrowheads indicate translocation breakpoints; small arrows show the inversion.

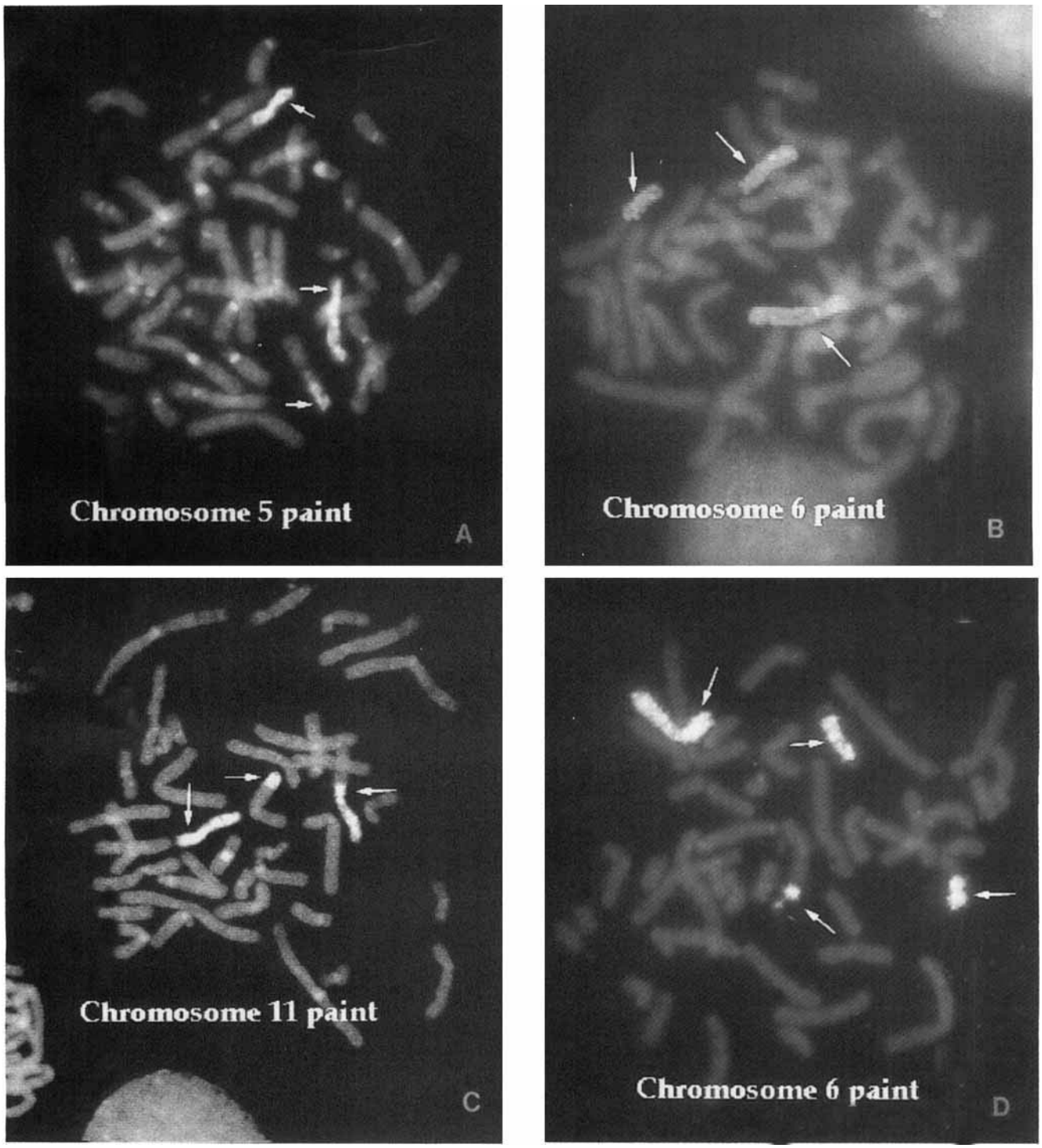

Fig. 2. Patient A: whole chromosome paint on metaphases with **A)** chromosome 5 specific library, **B)** chromosome 6 specific library, and **C)** chromosome 11 specific library. Patient B: **D)** whole chromosome paint on metaphase with chromosome 6 specific library. Arrows indicate painted chromosomal regions.

arrangement involving a balanced translocation between chromosomes 3 and 8 and a CCR involving chromosomes 6, 7, and 18. Parental chromosomes were normal. A repeat amniocentesis confirmed the original karyotype. Based on the cytogenetic findings the couple was counseled about the increased risk for mental retardation and/or congenital anomalies and they opted to continue the pregnancy. Ultrasound evaluations during the pregnancy failed to reveal any identifiable abnormalities. The infant was born at term by vaginal delivery with a birth weight of 2,813 g. He had a 2 day stay in the level II nursery due to a meconium plug.

At 4 months he had a prominent nasal root and metopic ridge, possible scoliosis, a barrel chest, and hypotonia. Based on irregular bowel movements and a protuberant abdomen by exam, a diagnosis of Hirschsprung disease was made and required surgery at age 6 months. A developmental evaluation at age 5 months showed gross motor skills in the 2 month range and fine motor skills in the 2–3 month range. Psychological evaluation documented borderline cognitive skills. At 18 months gross motor skills and speech were roughly at the 6 month level. In addition, at this age his head circumference was around the 3rd centile and his length and weight were at the 25th and 10th centiles, respectively.

Cytogenetic. Chromosome analysis on cultured amniocytes demonstrated an abnormal male karyotype with two independent chromosome rearrangements. The first was a reciprocal translocation between chromosomes 3 and 8. The second was a CCR involving single breaks on chromosomes 7 and 18 and two breaks on chromosome 6. The karyotype was interpreted as: 46,XY,t(3;8)(3qter→3p13::8q21.3→8qter;8pter→8q21.3::3p13→3pter),t(6;18;6;7)(6pter→p11.2::18q21→18pter;18qter→18q21::6p11.2→6q25::7q34→7qter;7pter→7q34::6q25→6qter) (Fig. 3). This karyotype was confirmed by peripheral blood chromosome analysis.

Whole chromosome painting. Whole chromosome paint for chromosome 6 clarified the three-way complex chromosome rearrangement by demonstrating the involvement of two translocations on the short and long arms of one chromosome 6. Chromosome 6 material could now be identified on two other chromosomes (Fig. 2D).

DISCUSSION

We describe two new cases of prenatally diagnosed apparently balanced de novo CCR. Both patients had some clinical abnormalities; patient A was small for gestational age and had some minor anomalies, while patient B had Hirschsprung disease and was developmentally delayed.

A review showed only six other prenatally diagnosed cases of apparently balanced de novo CCR. Bogart et al. [1986] first described a 3-way de novo apparently balanced translocation with a pericentric inversion. The pregnancy was continued and the child was phenotypically normal at birth. At age 2½ years, length fell below the 5th centile; however, development was appropriate with the exception of delayed speech. Kim et al. [1986] reported on an apparently balanced de novo CCR involving four chromosomes. The pregnancy was terminated and autopsy showed intrauterine growth retardation and other minor anomalies including low-set ears, widely spaced great toes, and hypoplastic mandible. The karyotype was confirmed on cultured skin and cord fibroblasts. Kohler et al. [1986] described a balanced de novo CCR involving two chromosomes. The pregnancy was continued and the patient was phenotypically normal and developmentally appropriate at age 2 years. Batista et al. [1993] described an apparently balanced de novo CCR involving four chromosomes and nine breaks. The pregnancy was terminated and an autopsy failed to show any identifiable anomalies. The prenatal cytogenetic findings were confirmed in fibroblasts. Most recently, Sikkema-Raddatz et al. [1995] reported on two new cases of prenatally diag-

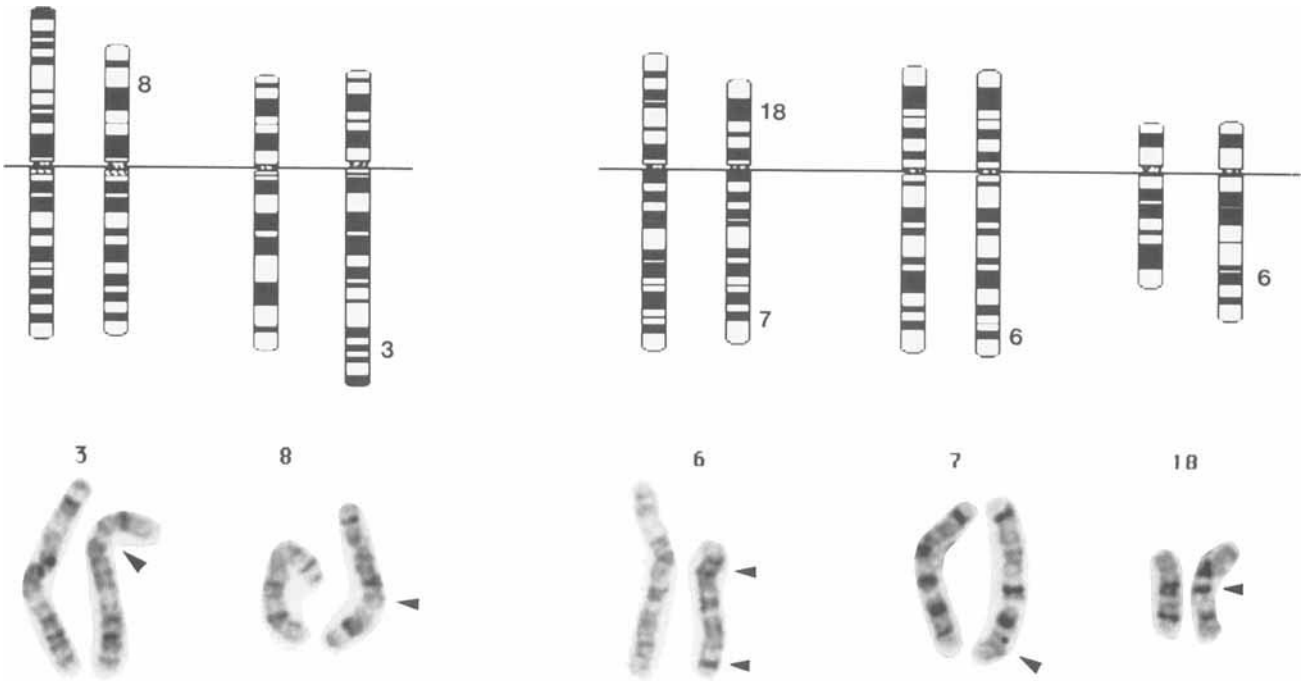

Fig. 3. Patient B: partial G-banded karyotype showing normal chromosomes 3, 6, 7, 8, and 18, a reciprocal translocation, and complex chromosome rearrangement. Arrowheads indicate translocation breakpoints.

TABLE I. Summary of Prenatally Ascertained Balanced De Novo Complex Chromosome Rearrangements*

Chromosomes	Number of breaks	Sex	Minor anomalies	CA	MR/DD	Reference
(6;5;11) inv(5)	4	M	+	+	−	Patient A
(3;8)(6;18;6;7)	6	M	+	+	+	Patient B
(3;4;10;17)	7	M	?	−	?	Sikkema-Raddatz et al., 1995
(2;5;18)	5	M	−	−	−	Sikkema-Raddatz et al., 1995
(1;3;4;9) inv der(1)	9	F	?	−	?	Batista et al., 1993
(4;15;16;6)	4	M	+	+	?	Kim et al., 1986
(7p;7q;14q)	3	M	−	−	−	Kohler et al., 1986
(6;11)(11;12) inv(6)	4	F	−	−	+	Bogart et al., 1986
Total			3/6	3/8	2/5	

*M, male; F, female; −, absent, +, present; ?, unknown/not reported; CA, congenital anomalies; MR, mental retardation; DD, developmental delay.

nosed balanced de novo CCR. The first was a CCR involving four chromosomes and seven breaks identified by CVS and later confirmed by amniocentesis. The pregnancy was terminated and an autopsy failed to show any abnormalities. The karyotype was also confirmed in skin fibroblasts. The second case was a CCR involving three chromosomes and five breaks. The pregnancy was continued. No congenital anomalies were present and follow-up at 3 years of age revealed normal growth and psychomotor development.

A summary of the prenatally ascertained balanced de novo CCR is presented in Table I. Of the eight cases, three had congenital anomalies and three of six cases had minor anomalies. Developmental delay was documented in two of the five cases where developmental histories were available.

In contrast to the prenatally diagnosed CCR, there have been numerous reports of balanced de novo CCR ascertained postnatally. Tables II and III review the postnatal cases with respect to the number of chromosome breaks. For the purpose of this review those patients with two independent balanced reciprocal translocations and those patients with a reciprocal balanced translocation and an inversion of a different chromosome were excluded. In addition, cases of apparently balanced CCR where parental karyotypes were not performed were also excluded.

A review of the postnatally ascertained balanced de novo CCR cases found some striking differences between patients in group I (Table II) and patients in group II (Table III). In group I, 45% (5/11) of patients were ascertained because of recurrent spontaneous abortions or infertility and did not have any minor abnormalities, congenital anomalies, or mental retardation/developmental delay. In contrast, only 6% (1/17) of patients in group II were ascertained because of recurrent spontaneous abortions and did not have any other abnormalities. The percentage of congenital anomalies was also markedly increased in group II when compared to group I (69% vs. 10%, respectively). Approximately 55% of patients in group I and 88% of patients in group II had either mental retardation or developmental delay. These findings suggest a possible relationship between the number of chromosome breaks

TABLE II. Summary of Postnatally Ascertained Balanced De Novo Complex Chromosome Rearrangements-Group I*

Chromosomes	Number of breaks	Sex	Minor anomalies	CA	MR/DD	SAB/INF.	Reference
(2;7;18)	3	F	−	−	−	SAB	Timár et al., 1991
(1;11;12)	3	M	+	+	+		McCombs et al., 1990
(2;11;18)	3	F	−	−	−	SAB	Gardner et al., 1986
(3;5;11)	3	F	−	−	−	SAB	Smith et al., 1985
(4;7;15)	3	M	−	−	−	INF	Chandley et al., 1975
(1;7;21)	4	M	−	−	+		Lopreiato and Wulfsberg, 1992
inv(1) inv ins(1;3)	4	M	+	−	+		Voullaire and Webb, 1988
(3;9)(3;18)	4	F	+	−	+		Hall and Hart, 1986
(5;1;10;12)	4	M	−	−	−	INF	Rodriguez et al., 1985
(2;14;21)	4	M	+	−	+		Fryns et al., 1984
(1;3)(3;9)	4	F	?	?	+		Jacobs et al., 1974
Total			4/10	1/10	6/11	5/11	

* F, female; M, male; +, present; −, absent; ?, unknown/not reported; SAB, spontaneous abortion; INF, infertility.

TABLE III. Summary of Postnatally Ascertained Balanced De Novo Complex Chromosome Rearrangements-Group II*

Chromosomes	Number of breaks	Sex	Minor anomalies	CA	MR/DD	SAB/INF.	Reference
(1;11;2;5) inv(1)	5	F	−	−	−	SAB	Kausch et al., 1988
(2;3;4)(2;5)(4;10)(3;10)	5	F	+	+	+		Kitsiou et al., 1987
(3;8;11)	5	M	+ (TRP)	+	+		Sanchez et al., 1985
(1;3;5)	5	M	−	+	+		Fryns et al., 1984
(2;4;7)(7;8)	5	M	+	−	+		Couzin et al., 1983
(2;3;11;12)	6	F twins	+	+	+		Wakita et al., 1992
(2;3)(3;12)(4;6)	6	M	+	+	+		Del Porto et al., 1991
(2;3;16) ins(6;7)	6	M	+	−	+		Till et al., 1991
(1;7)(5;9)(13;16)	6	M	−	+	+		Watt and Couzin, 1983
(1;8)(2;4)(4;8)	6	F	+	−	+		Kleczkowska et al., 1982
inv ins(X;1) inv (1)(X;1)(7;13)	6	F	+	+	+		Seabright et al., 1978
(1;7)(4;15)(4;12)	6	F	+	−	+		Fitzgerald et al., 1977
(1;5;9) inv ins(8)	6	F	+	+	?		Martinetti and Noel, 1973
(1;2)(6;10) dir ins(3;5)	7	F	−	?	+		Kamei et al., 1988
(7;21;14) dir ins(10;21)	7	F	+	+	−		de Asis et al., 1984
(X;3;7;21)	7	F	+	+	+		Pai et al., 1980
(2;3) with insertions	7	M	+	+	+		Fitzgerald, 1974
Total			13/17	11/16	14/16	1/17	

* M, male; F, female; +, present; −, absent; ?, unknown/not reported; SAB, spontaneous abortion; INF, infertility; TRP, trichorhinophalangeal syndrome.

TABLE IV. Summary of Balanced De Novo CCR*

	Postnatal			
	Group I	Group II	Total	Prenatal
Dysmorphic	40% (4/10)	76% (13/17)	63% (17/27)	50% (3/6)
Congenital anomalies	10% (1/10)	69% (11/16)	46% (12/26)	38% (3/8)
MR/DD	55% (6/11)	88% (14/16)	74% (20/27)	40% (2/5)
Hx.-SABs or infertility	45% (5/11)	6% (1/17)	21% (6/28)	NA

* MR, mental retardation; DD, developmental delay; Hx., history; SABs, spontaneous abortions.

and phenotypic effects. Table IV summarizes the comparison of these findings between the prenatally and postnatally ascertained cases.

Molecular cytogenetic techniques have clarified complex chromosome abnormalities found by routine or specialized banding techniques. Application of whole chromosome paints have represented a major cytogenetic advancement that has facilitated the accurate identification of CCR [Van Der Burgt et al., 1992; Batista et al., 1993, 1994; Verma et al., 1993; Wang et al., 1993].

When confronted with a prenatally diagnosed CCR whole chromosome painting will help elucidate the nature of the chromosome rearrangements. In our two cases this technique helped delineate the CCR. Using traditional cytogenetics, our initial impression of the karyotype in case B was that of an unbalanced CCR with a deletion. Whole chromosome painting reinterpreted this CCR as balanced.

Most patients with postnatally ascertained balanced de novo CCR have multiple congenital anomalies, mental retardation/developmental delay, and/or minor anomalies. There is a subset of patients who is phenotypically normal and was ascertained due to infertility or recurrent pregnancy loss. However, most of these have four or fewer breaks (group I CCR).

The paucity of information regarding prenatally diagnosed CCR and the bias of ascertainment of postnatal CCR cases pose problems in counseling families. More information regarding the outcome of prenatally ascertained apparently balanced de novo CCR is required for accurate risk assessment.

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